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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/922,958	08/07/2001	Lorenz Poellinger	3743/49008	9818

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/922,958	POELLINGER ET AL.	
	Examiner	Art Unit	
	Brandon J Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) *1-32,37-39 and 43-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-36 and 40-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: _____.

Poellinger *et al.*
Date of Priority (Claims 33-36): 8/07/2000
Date of Priority (Claims 40-42): 8/07/2001

DETAILED ACTION

Election/Restrictions

The response filed on August 7, 2004 to the restriction requirement of June 14, 2004 has been received. Applicant has elected Group VI, drawn to a method for screening for an antagonist of the PYI motif or P564 spanning protein, which encompasses claims 33-36 and 40-42. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a).

Claims 1-66 are pending.

Claims 1-32, 37-39 and 43-66 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Thus, claims 33-36 and 40-42 are currently under examination.

The substitute specification filed 12/03/2001 is acknowledged and has been entered.

Priority

A review of the provisional application serial number 60/223480 did not lend support for the disclosure of a method of evaluating an antagonist of the PYI motif or P564 spanning protein for VHL-HIF-1 alpha interaction inhibiting efficacy. If applicant disagrees with any rejection of claims 40-42 set forth in this office action based on examiner's establishment of a priority date of **August 7, 2001** for the instant claims in application serial number 09/922,958 applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Specification

The disclosure is objected to because of the following informalities: On page 9, paragraph 0026, the specification discloses a polypeptide having the amino acid sequence of SEQ ID NO: 5 or a smaller fragment thereof SEQ ID NO: 6 (residues 547-575, Fig. 28). The sequence listing filed on August 7, 2001 contains an oligonucleotide sequence represented as SEQ ID NO: 6 and is silent on the amino acid sequence set forth in the specification as SEQ ID NO: 6. In addition, Figure 28 does not appear to define what SEQ ID NO: 6 is and only conveys luciferase activity of GAL4-NTAD mutant in 293 cells under normoxic conditions and hypoxic conditions (page 18, paragraph 0078). In addition, Figures 11, 26, and 29 appear to be directed to multiple amino acid sequences, which do not include sequence identifiers. Lastly, the specification on page 7 (paragraph 0019) and page 13 (paragraph 0042) disclose two different ninth aspects of the present invention, i.e. a product and method respectively.

Appropriate correction is required.

Claim Objections

Claim 33 is objected to because of the following informalities: Claim 33 refers to an isolated protein according to claim 29, which is a non-elected invention. Appropriate correction is required.

Note: Any rejection made to Claims 33-36 in this Office action are under the presumption that the isolated protein according to claim 29 is the isolated polypeptide of Claim 1 comprising an amino acid sequence of SEQ ID NO: 4 and fragments thereof with an altered PYI motif at residues 564-566. In addition, all references made to the specification are meant to reflect the substitute specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-36 and 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 33-36 are rejected as vague and indefinite for reciting the term N-TAD in association with screening for an agent that modulates its function as the sole means of identifying the claimed molecule. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. The rejection can be obviated by amending the claims to specifically and uniquely identify N-TAD, for example, by SEQ ID NO. and function of N-TAD.

Claims 40-42 are rejected as vague and indefinite for reciting the term p564 spanning protein in association with evaluating for an antagonist as the sole means of identifying the claimed molecule. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. The rejection can be obviated by amending the claims to specifically and uniquely identify p564 spanning protein, for example, by SEQ ID NO. and function of p564 spanning protein.

Claims 40-42 are rejected as being vague for reciting the term "normal" in association with a level VHL-HIF-1 alpha interaction. The term "normal" is not defined by the claim or specification and one of ordinary skill in the art would not be reasonably apprised of the standard for determining what is a normal level.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-36 and 40-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention. As set forth previously, "an isolated protein according to claim 29" is the isolated polypeptide of Claim 1 comprising an amino acid sequence of SEQ ID NO: 4 and fragments thereof with an altered PYI motif at residues 564-566. In the instant case, claims 33-36 are inclusive of a genus of molecules identified as comprising an amino acid sequence set forth in SEQ ID NO: 4 or any fragments and/or mutants thereof that bind to a genus of target proteins and fragments thereof referred to as "VHL". While claims 40-42 are inclusive of a genus of molecules referred to as having a "PYI motif" or functional fragments thereof and a genus of molecules referred to as "P564 spanning protein" or functional fragments thereof. However, the written description only sets forth two fragments of SEQ ID NO: 4 (SEQ ID NOs: 5 and 6), each of which comprise a PYI motif or p564 spanning protein, used together with VHL (SEQ ID NO: 2) for methods of identifying agents.

The specification teaches (page 9, paragraph 0026-0027) that methods for identifying agents of the present invention includes, but is not limited to, polypeptides having at least an amino acid of SEQ ID NO: 5 (minimum N-TAD) or a smaller fragment thereof, SEQ ID NO: 6 (residues 547-575), or described mutants thereof and the VHL protein (SEQ ID NO: 2). With regards to the mutants, the specification teaches (Pages 6-7) that the mutants comprise altered amino acid residues such as; an altered PYI motif at residues 564-566, a ^{564}P, a $^{565\text{-}566}$YI, ^{565}Y, a $^{569\text{-}571}$DDD, ... ect.. The specification further teaches (page 13, paragraph 0042) that additional methods for identifying agents of the invention include, but are not limited to, polypeptides comprising a PYI motif or p564 spanning polypeptide (residues 547-575) or portion thereof. Thus, it appears that a p564 spanning polypeptide consists of the same amino acids as disclosed for SEQ ID NO: 6. However, the written description only sets forth two fragments of SEQ ID NO: 4 (SEQ ID NOs: 5 and 6), each of which comprise a PYI motif or p564 spanning protein, used together with VHL (SEQ ID NO: 2) for identifying agents. Therefore, the written description does not commensurate with the full scope of any fragments and/or variants of SEQ ID NO: 4 or any fragments of the VHL protein (SEQ ID NO: 2).

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus."

See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of molecules that bind VHL nor does it provide a description of structural features that are common to SEQ ID NO: 4. Further, the specification fails to provide a representative number of molecules referred to as VHL along with a description of structural features that are common to the VHL. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of all the fragments of SEQ ID NO: 4 and VHL, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable

due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a VHL protein (SEQ ID NO: 2) and two fragments of SEQ ID NO: 4,(SEQ ID NOs: 5 and 6), which comprise the PYI motif and p564 spanning protein, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 40-42 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for evaluating an antagonist of the PYI motif or P564 spanning protein in a cell or group or cells, does not reasonably provide enablement for evaluating an antagonist in any and all organisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn broadly to a method of evaluating an antagonist of the PYI motif or P564 spanning for VHL-HIF-1 alpha interaction inhibiting efficacy, comprising:

determining a normal level of VHL-HIF-1 alpha interaction in a cell, group of cells, or an organism for detecting any cancer; administering said antagonist to an equivalent test cell, group of cells, or organism, than measuring the VHL-HIF-1 alpha interaction; and determining if the antagonist is efficacious when the measured test level of VHL-HIF-1 alpha interaction is less than the normal level.

Thus, it appears that this would include evaluating an antagonist *in vivo* by administering an antagonist to any and all types of organisms including, but not limited to, mammals.

However, one cannot extrapolate the teachings of the specification with the scope of the claims because the claims are drawn to an *in vivo* system for evaluating an antagonist in any and all organisms. The specification provides insufficient guidance and or objective evidence the claimed method for evaluating an antagonist of the PYI motif or P564 spanning protein for VHL-HIF-1 alpha interaction inhibiting efficacy could be practiced *in vivo* in an organism. The specification teaches (page 18-45), through examples 1-9, a number of different *in vitro* methods. The specification further discloses (page 31, paragraph 0119) an *in vivo* ubiquitination experiment conducted using FLAG-tagged wild type or mutant N-TAD in order to investigate the mechanism of VHL-mediated degradation of HIF-1 alpha. Although, the specification does disclose an *in vivo* ubiquitination experiment, it appears not to provide any experimental conditions as to how to evaluate a PYI motif or P564 spanning protein antagonist *in vivo*. The specification appears to be silent on how to determine what a normal level of VHL-HIF-1 alpha interaction is in any and all organisms. Would the normal level be different in a rat versus a human versus a rabbit? In addition, the specification appears not to disclose how the antagonist is administered to the organism or at what dose. Is the antagonist administered to an organism intravenously, intramuscularly, subcutaneously, transdermally, or by inhalation? Furthermore, the specification appears to be silent on how to measure the level of VHL-HIF-1 interaction in an organism once the antagonist is administered and how to determine if the antagonist is efficacious when the measured test level of VHL-HIF-1 alpha interaction is less than the normal level.

Those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking.

The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in- vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
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BF

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